

### **REMARKS**

Claims 1-8, and 11, all of the pending claims in this application, are rejected in the Office Action dated February 20, 2008. Applicants, in a separate paper, submit herewith a declaration by Cornelis Marius Timmers, providing more detailed analytical data for the compounds prepared according to the Examples of the present application. Applicants respectfully request reconsideration of the claims in view of the following remarks.

#### **Claims are Enabled.**

Claim 11 is rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, the specification, while enabling for inhibition of FSH receptor activity and the corresponding decrease in fertility, does not reasonably provide enablement for modulation of FSH receptor activity or regulation of fertility. The Examiner thus asserts that the specification does not enable a person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the pending claims. The Examiner concludes that the claims taken together with the specification imply that by administering the composition of claim 8, the skilled artisan can increase or decrease FSH receptor activity and increase or decrease fertility. According to the Examiner the specification has provided guidance for antagonism of FSH with the claimed compounds on page 40, example 44 but does not provide guidance for how to use the claimed compounds as FSH agonists. Further, in response to applicants' arguments that example 44 provides guidance for both agonistic activity and antagonistic activity, the Examiner asserts that this example includes the very general statement that "[c]ompounds of all examples exhibited an  $EC_{50}$  ( $IC_{50}$ ) value of less than  $10^{-5}M$  in either agonist or an antagonist assay set-up or both," and no data to support this statement is provided. According, to the Examiner it is unclear how one compound could both stimulate and suppress fertility at any given concentration, considering the complete lack of specific data regarding the assays and concentrations being tested.

In response applicants submit that in contrast to the Examiner's assertion, example 44 on page 40 provides guidance for both agonistic as well as antagonistic activity, particularly when read in light of the specification page 16, line 17 to page 18, line 16. More specifically, the specification

on page 17, lines 22-27 provides an assay for the determination of agonist activity while on page 17, line 28 to page 18, line 4 it provides an assay for the determination of antagonist activity. Further, the specification provides in Example 44 methods of determining the activity (whether it be as an agonist or antagonist) for each of the disclosed examples and provides data describing the activity. As described, activity (with respect to the FSH receptor) of compounds of formula I was measured with a cAMP responsive element/promoter directing the expression of a reporter gene (luciferase), wherein binding of a ligand (compound) to the FSH receptor will result in an increase (for an agonist) of cAMP and therefore increased expression of the reporter gene. Thus, this description in Example 44 clearly describes determining agonistic properties of the claimed compounds, the description of another assay describes testing their antagonistic properties. In the declaration by Cornelis Marius Timmers (the "Timmers declaration") submitted herewith the agonist/antagonist data for each of the examples described in the application are shown in Table 1. The data in Table 1, as it appears in the Timmers declaration, was obtained when the claimed invention was made and provided the basis for the statement in Example 44 with respect to the agonist/antagonist activity without actually including the table itself in the specification of the current application.

Thus, applicants submit that the claimed tetrahydroquinoline derivatives of formula I are shown to be ligands (either as agonist, antagonist or both) for the FSH receptor, as demonstrated in Example 44 of the specification of the currently pending application and in Table 1 of the Timmers declaration. With respect to some compounds having both agonistic as well as antagonistic activity, the Timmers declaration provides the explanation that some compounds may have both agonistic and antagonistic activity as a function of their concentration. Further, the assay determining efficacy of the claimed tetrahydroquinoline derivatives as either an agonist or antagonist for the FSH receptor relies on cAMP accumulation. Activation of the FSH receptor with FSH has previously been correlated with cAMP accumulation. FSH receptor activation with FSH is a well described pathway in regulating fertility. Thus, applicants submit there is a clear nexus between the observed activity of the claimed tetrahydroquinoline derivatives of formula I and a method of regulating fertility. For these reasons, applicants submit that the specification provides an enabling disclosure for the claimed tetrahydroquinoline derivatives of formula I describing a method for determining as well as showing either inhibition or activation of the FSH receptor activity and

Application No. 10/540,335  
Amendment dated June 6, 2008  
Reply to Office Action of February 20, 2008

Docket No.: 2002.749US

thereby also the corresponding decrease and increase in fertility. Thus, applicants submit that the skilled artisan reading the disclosure of the currently pending application would know how to make and/or use the claimed invention of claim 11, providing an enabling disclosure to the skilled artisan for the modulation of the FSH receptor or regulation of fertility. Accordingly, applicants submit that claim 11 is clearly enabled by the specification as filed and respectfully request withdrawal of the rejection of claim 11 under 35 U.S.C. §112, first paragraph.

Double Patenting Rejection.

Claims 1-8, and 11 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 2, 9, 13, and 16 of co-pending application 10/540,336. Applicants defer responding to the rejection until such time as any of the above claims is allowed at which time applicants, although disagreeing with the Examiner's assertions, intend to submit a proper Terminal Disclaimer.

In view of the above amendment, applicants believe the pending application is in condition for allowance. If the Examiner believes a telephone conference would be of value, she is requested to call the undersigned at the number listed below. Applicants respectfully request the issuance of a timely Notice of Allowance in the case.

Dated: June 6, 2008  
Organon International Inc.  
Patent Department  
c/o Schering-Plough Corporation  
2000 Galloping Hill Road  
Kenilworth, New Jersey  
K-6-1; MS 1990  
Tel: (908) 298-2161  
Fax: (908)-298-5388

Respectfully submitted,

By 

Susan Hess  
Registration No.: 37,350  
Attorney For Applicant(s)